HOW EFFECTIVELY TO USE BIOPHYSICAL MODELS IN TREATMENT PLANNING?

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INTRODUCTION

In any radiotherapy treatment, changes in either the dose-rate or pattern of fractionation will induce changes in the radiobiological response of normal tissues and tumours. In mixed modality regimen an assessment of the overall biological effect cannot be determined simply by summing the physical doses instead it is necessary to make use of the concept of Biologically Effective Dose (BED) (Barendsen, 1982, Fowler, 1989).

A number of papers have drawn attention to the potential value of the linear-quadratic (LQ) model as an aid for solving problems related to the „iso-effectiveness" of differing radiotherapy regimen (Dale, 1986; Dale, 1989; Dale, 1990; Dale, 1990;Fowler, 1989; Matula and Durovec, 1991). However, normal tissue responses are not governed solely by the pattern of dose delivery - they depend also on the volume of the organ irradiated. Furthermore, commonly used „reference schemes" may not represent the tolerance dose of a given tissues - they may be sub-tolerance and therefore provide an unnecessarily conservative limitation in the design of an alternative scheme.

The graphical representation of tissue response suggested by Burman et al (Burman et al, 1991; Kutcher et al, 1991; Lyman and Wolbarst, 1989) can be used as a quantitative basis for generating analytical functions with which to describe the volume effect, and therefore offer scope for a more exact evaluation of radiobiological effects in radiation therapy.

The aim of this contribution is to give:

- a review about the current state using the Linear-quadratic model (LQ) for assessment biological effects in complex radiation therapy (brachytherapy + external beam therapy)
- introduction to the estimating of the NTCP (normal tissue complications probability including a volume factor) and the TCP (tumour control probability)
- presentation of illustrative examples of simulation of effects (through parameters BED, NTCP and TCP) for rival radiotherapy treatment protocols.

Key words: Biophysical modelling, Linear-quadratic model, BED Relative Effectiveness, Repopulation, Reparation, NTCP, TCP, Volume factor, Dose-volume histograms, Intracavitary therapy, External beam radiation therapy (EBRT).

RADIOBIOLOGICAL BACKGROUND

The linear quadratic formalism

The linear quadratic formalism was originally described for the formation of chromosome aberrations. The application to radiation therapy has recently been reviewed by Fowler (Fowler, 1989) Dale (Dale, 1986; Dale, 1989; Dale, 1990; Brenner et al, 1995) and many others.
In this approach the cellular survival, S, at a dose D is written as

$$S(D) = \exp\left(-\alpha D - \beta D^2\right) = \exp\left(-E\right) \quad (1)$$

Two terms in the exponent (Eq.1) indicate that the two elementary damaged species may be produced by the passage of the same tract of radiation (linear term in dose) or by two different tracts (quadratic term)

Including of repair to the LQ model

Clearly, if some time elapses between the passage of the first and second tracts, there exists the possibility of the first site being repaired before interacting with the second. The repair will result in a reduction of the second, quadratic term in Eq. 1 by a factor denoted the „G" :

$$S(D) = \exp\left(-\alpha D - G\beta D^2\right) \quad (2)$$

where a and ß are specific parameters of radiosensitivity (for tumour or normal tissues) described below. G is a complex tissue specific parameter and relates to the rate of repair of

sublethal damage under conditions of the treatment. For more details see (Brenner et al, 1995; Dale , 1989; Dale, 1990; Dale, 1990).

Including of repopulation to the LQ model

The LQ formalism can take into account the effects of tumour repopulation (as well as repopulation in normal tissues) i.e. effects on tumour changes and damages in the overall time.

$$S(D) = \exp\left(-\alpha D - G\beta D^2 + \frac{T - t_0}{T_{pot}}\right) \quad (3)$$

T - overall treatment time (days)
t_0 - the delay (days) before which tumour repopulation or compensatory tissue repopulation begins.
T_{pot} - potential doubling time (days)

Including of redistribution and reoxygenation

The extension of the LQ model to include the cell cycle redistribution and reoxygenation has been described by (Brenner et al, 1995). In this approach redistribution and reoxygenation are both regarded as aspects of a single phenomenon, which has termed as „resensitization". The general formula of the LQ model becomes:

$$S(D) = \exp\left(-\alpha D - G\beta D^2 + G\frac{\sigma^2}{2}D^2 + \frac{T - t_0}{T_{pot}}\right) \quad (4)$$

Modelling combined effects of repair, resensitization and repopulation with explanation is shown on the Figure 1.

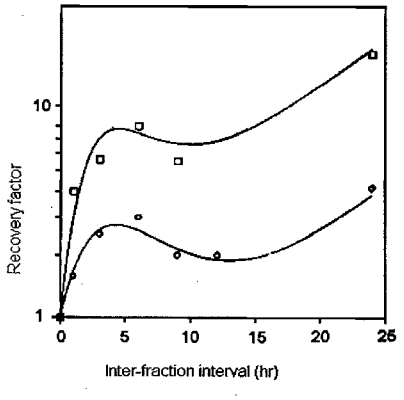

Fig. 1

Modelling combined effects of repair, resensitization and repopulation. Data points are from Belli et al. (2) for P-388 tumors exposed in vivo to two acue doses separed by the tiem shown on the horizontal axis. Recovery factor is the ratio of clonogenic survival to that for zero time separation.

◊ and lower curve hypoxic tumors exposed to 15 Gy + 15 Gy

□ and upper curve aerobic tumors exposed to 5 Gy + 5 Gy.

The curves are fitted from the LQ model by Eq.4
For small interfraction times there is a characteristic rise of recovery factor, attributed to repair of sublethal lesion; at larger times there is a decrease, attributed in the model to re-sensitization, the final rise then being attributed to repopulation.

Biologically Effective Dose

For specific case of fractionated treatment and HDR brachytherapy when : T >> t_{repair} and interfraction interval > 6 hours G yields 1 and $\sigma^2/2$ represents a correction less 1% of the linear term then we can describe the exponent E in the Eq. 4 into a simple formula:

$$BED = \frac{E}{\alpha} = Nd\left(1 + \frac{d}{\alpha/\beta}\right) - K(t - t_0)$$

$$RE = \left(1 + \frac{d}{\alpha/\beta}\right) \quad (5)$$

where:

BED - Biologically Equivalent Dose (in Gy),
RE - Relative effectiveness of a radiation treatment, N - number of fractions, d - dose per fraction [Gy], α/β - the parameter of intrinsic, radiosensitivity for the selected tissue (tumour or normal tissues) [Gy], $K = 0.693/\alpha T_{pot}$ [Gy/day].

Average values of parameters

In general, the α/β ratio (whose unit of measure is the gray) has a value found:
3 - 5 Gy for late reacting normal tissues and
10 - 30 Gy for tumours and early reacting normal tissues.
The relative effectiveness (RE) of the treatment depends on the size of dose per fraction and on the responding α/β ratio. The changes of the effects with size of the dose/fraction and the α/β ratios are shown on the Fig. 2.

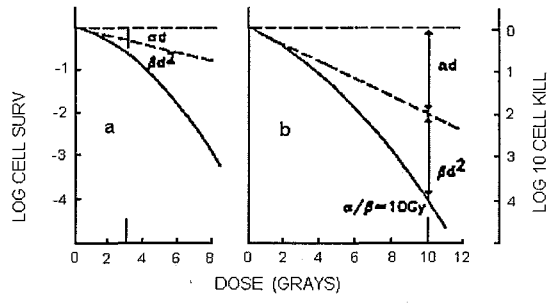

Fig.2
Linear-quadratic dose-response curves for early and late effects with illustration of definition for the α/β ratio.

The consequences of repopulation

The biological effect on the tumour is likely greater in fractionated regimen if the treatment is kept reasonably short (i.e. if the treatment is accelerated).
The effect will also be enhanced if the tumour is characterised by a high radiosensitivity and/or a large potential doubling time (i.e. if it divides slowly)
Values of „K" vary from:
0 - 0.1 Gy/day for late reacting tissues,
0 - 0.3 Gy/day for early reacting tissues
0 - 0.6 Gy/day for tumours
The repopulation is initially slowed up until a certain time (t_0) (typically 14 -28 days) after which it accelerates. Repopulation for late reacting tissues can be nearly neglected.

Linear-quadratic formalism for continual brachytherapy

In low/medium dose-rate (LDR/MDR) brachytherapy the relevant equation derivated from Eq. 4 is:

$$BED = RT\left(1+\frac{2R}{\mu\,\alpha/\beta}\right) \qquad (6)$$

where:
R - dose rate in [Gy/h]
T - treatment time [hours]
μ - repair constant [h^{-1}]
Typical values used for μ:
0.46 h^{-1} for late-reacting tissues (responding to a half-time for repair of 1.5 h)
0.46 - 1.4 h^{-1} for tumours and early-reacting tissues (responding to half-times in the range 1.5- 0.5h.

Comment: The Eq. 6 is specific form of more general equations which are applied to more complex treatment regimen, eg. those involving short interfraction intervals e.g. PDR brachytherapy or short intervals between fractions in HDR and EBRT (Brenner et al, 1995). For more details see papers (Brenner et al, 1995; Dale, 1986; Dale, 1989)
Conclusion

The mechanisms of changes on tumour cell population and normal tissues, characterized by well known „four R's" of radiobiology (Repair, Repopulation, Reoxygenation and Redistribution) can be now described by the extended LQ model.
There are still strong requests on experimental and clinical studies to precise parameters in the LQ model.

Equalizing schemes using concept of the LQ model

In general two schemes (A) and (B) are iso-effective in their radiation effects on a selected tissue if the tissue-specific BED's are identical.

$$BED_{\alpha/\beta}\,(A) \quad = \quad BED_{\alpha/\beta}\,(B) \qquad (7)$$

For treatments composed of a number of individual courses (e.g. EBRT + brachytherapy) the BED's associated with the individual components may be summed to give an overall measure of biological effect.
In order to be unambigueous as to which tissue effects are being discussed, it is useful to assign a subscript after the BED in accordance with the α/β value which has been selected for the calculations (eg. BED_3, BED_{10}, etc) (Fowler, 1989).

Ilustrative example:
What is the relative effectiveness RE and BED for daily fractionation 30F/2Gy for tumour and late reacting tissues in comparison with hyperfractionation applied with the same total dose (60 Gy) but in 40 Fr/1.5Gy/both in day.

Calculation:
Using Eq. 5 and α/ß = 10 Gy for tumour and 3 Gy for late reacting tissues we can get:

Daily fractionation	Hyperfractionation
RE_{10} = 1 + 2/10 = 1.2 RE_3 = 1 + 2/3 = 1.66 BED_{10} = 72 Gy BED_3 = 99.6 Gy	RE_{10} = 1 + 1.5/10 = 1.15 RE_3 = 1 + 1.5/3 = 1.5 BED_{10} = 69 Gy BED_3 = 90 Gy

Conclusion:
Hyperfractionation has a lower effect on tumours (less at 4%) but an impressive „saving" effect on late reacting tissues (at 10%) !
However, the higher or lower value of the BED for late effects does not give an answer how the percentage will increase or decrease of complications in comparison with the reference scheme. This information can be achieved using concept of the NTCP explained below.

CALCULATION OF NTCP

Lyman's model for daily fractionation

The normal tissue complication probability can be described by the model introduced by J. Lyman (Lyman and Wolbrast, 1989)

$$NTCP = \frac{1}{2\pi}\int_{-\infty}^{t}\exp\left(\frac{t^2}{2}\right)dt \qquad (8)$$

$$t = \frac{D_{appl} - TD_{50}(v)}{mTD_{50}(v)}$$

where:

v - V/V_{ref}
V - partial organ volume irradiated
V_{ref} - whole organ volume, respectively

$$TD(v) = TD(1).\ v^{-n} \qquad (8a)$$

n - specific organ volume parameter
m - specific organ dose parameter
D_{appl} - total applied dose to tissue
TD_{50} - dose related to produce 50% of complication

The parameters n, m, $TD_{5/5}$, $TD_{50/5}$ for 29 normal tissues and end points have been chosen from the paper Burman et al. (Burman et al, 1991; Kutcher et al, 1991).

In this paper they have compiled clinical tolerance data for 29 normal tissues and fitted it to sigmoid-type curves in order to represent the response when daily fractionation is used. The difference in response between uniform and partial irradiation is expressed as a function of the delivered dose and the volume irradiated by means of Lyman's 4-component model (Lyman and Wolbrast, 1989).
There are shown analytic functions representing complication probabilities vs. dose and volume for rectum and bladder on the Figures 3.a) and 3.b).

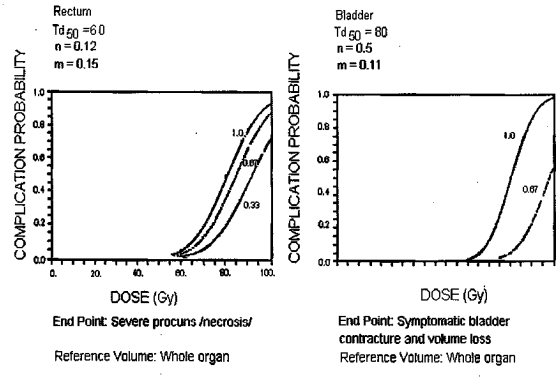

Fig. 3
Fitted curves of complication probabilities NTCP depending on dose and irradiated volume of tissue for 3 fixed values of partial volume: 1 - whole volume, 2/3 and 1/3 volume (reproduced with permission from Burman et al. (4))

Generalisation of Lyman s model to non-daily fractionation

The Eq. 8 may be applied for any other (non-daily fractionation) regimen, when „t" is re-defined as:

$$t = \frac{BED_{appl} - BED_{50}(v)}{mBED_{50}(v)} \qquad (9)$$

This generalisation of Lyman s model enables to estimate predictive values of NTCP in any treatment modalities and their combinations. Respecting to relations in equation (8) for:

$$v = V / Vref.$$

and

$$BED(v) = BED(1)^{-n}$$

it is possible to determinate „Effective partial volume" (from dose volume histogram), and then, to calculate particular BED and NTCP.
The associated radiobiological parameters taken from a set of the latest papers (Belli et al,

1967; Fowler, 1984; Fowler, 1984; Fowler, 1989; Kutcher et al, 1991) and calculated $BED_{5/5}$ (i.e. BED related to NTCP = 5% / 5 years) and $BED_{50/5}$ (related to NTCP = 50% / 5 years) are summarized in the Table 1.

Table 1. The radiobiological data of the normal late reacting tissues collected from papers (Trott and Kummermehr, 1985; Fowler, 1989; Kutcher et al, 1991) as a data-base to the program.

Normal tissue	Clinical end point	$TD_{5/5}$ [Gy]	α/β [Gy]	Fr.	T days	n	m	$BED_{5/5}$ [Gy]
Bladder	contracture,loss	65	5	33	45	0.5	0.11	91.0
Brach.Plexus	clin.nerv.damage	60	5	30	40	0.03	0.12	84.0
Brain stem	necrosis,infarct.	50	2.5	25	33	0.16	0.14	90.0
Brain	necrosis,infarct	45	2.5	22	30	0.25	0.15	79.2
Cauda equina	nerve damage	60	2.5	30	40	0.03	0.12	108.0
Colon	perfor.,fistula	45	5	22	30	0.17	0.11	61.6
Ear-middle	chron.ser.otitis	55	5	27	37	0.01	0.09	75.6
Esophagus	perfor.stricture	55	5	27	37	0.06	0.11	75.6
Eye-lens	cataract.-interv.	10	1.2	5	5	0.3	0.27	22.7
Eye-opt.nerve	blidness	50	1.2	25	33	0.25	0.14	133.3
Eye-retina	blidness	45	1.2	22	30	0.20	0.19	117.3
Femoral H N	necrosis	52	5	26	36	0.25	0.12	72.8
Heart	peri .pancarditis	40	3	20	26	0.35	0.10	66.7
Intestine	obstruct.perforat.	40	5	20	26	0.15	0.16	56.0
Kidney	clin.nephritis	23	4.1	11	15	0.70	0.10	32.7
Larynx	cartilag.necros.	70	3.8	35	47	0.11	0.07	106.8
Larynx	laryng.edema	50	3.8	25	33	0.08	0.17	76.3
Liver	failure	30	3	15	19	0.32	0.15	50.0
Lung	chron.pneumonitis	17	3.7	9	11	0.87	0.18	27.0
Parotid	xerostomia	32	5	16	22	0.70	0.18	44.8
Rectum	sev.proct.necros.	60	5	30	40	0.12	0.15	84.0
Rib cage	pathol.fracture	44	5	22	30	0.10	0.21	61.6
Skin	necros. ulcerat.	55	3.7	27	37	0.10	0.12	83.3
Spin.cord c.	myelitis,necros.	46	2.5	23	31	0.05	0.17	82.8
Spin.cord l.	myelitis necros.	46	5.2	23	31	0.05	0.17	63.7
Stomach	perfor.,ulcerat.	50	3	25	33	0.15	0.14	83.3
Thyroid	clin.thyroiditis	46	5	23	31	0.22	0.26	64.4
TM joint	limited function	60	5	30	40	0.07	0.10	84.0

Comments: $TD_{5/5}$ - total dose related to NTCP = 5% during 5 years. For all late reacting normal tissues: $\mu = 0.46\ h^{-1}$, K = 0.01 Gy/day. Starting of repopulation after 60 days, finishing of repopulation 100 days.

As the calculation using BED, TCP and NTCP concepts is highly time-consuming, we have developed a comprehensive computer program RADBIO which renders many options for flexible calculation all radiobiological parameters explained above.

Using the program there can (in a „user-friendly" dialogue) be input the treatment and dosimetric data of applied protocols and to get the results in the form of a comprehensive radiobiological report (see Table 2). The application of BED, NTCP and TCP is demonstrated on several examples.

Table 2. The ouput of the program RADBIO - an illustrative example

RADIOBIOLOGICAL PATIENT REPORT				
NAME OF PATIENT :		X.Y. by protocol for Ca uter.cervix		
Selected tissue:		TUMOR RESP. CERV.CORP.	LATE EFF. RECTUM	LATE EFF BLADDER
Alfa/beta ratio [Gy]:		13.90	5.00	5.00
Repair. half time [Hour]:		0.50	1.51	1.51
Repopul. factor [Gy/Day]:		0.30	0.01	0.01
BED reference [Gy]:		75.54	84.20	89.76
LOG CELL KILL reference:		9.85	10.98	11.70
APPLIED COURSE	NAME :	EBRT 24F/1.7Gy/day 2AP/PA		
Number of fractions:		24	24	24
Dose / fraction [%]:		95.00	90.00	90.00
Dose / fraction [Gy]:		1.70	1.61	1.61
Treatment time [Days]:		33	33	33
Whole dose [Gy]:		40.80	38.64	38.64
Treatment gap [Days]:		10	10	10
BED applied [Gy]:		37.09	51.25	51.25
LOG CELL KILL:		4.84	6.68	6.68
APPLIED COURSE	NAME :	4F HDR 6Gy/A/2F/week		
Number of fractions :		4	4	4
Dose / fraction [%]:		100.00	75.00	80.00
Dose / fraction [Gy]:		6.00	4.50	4.80
Treatment time [Days]:		11	11	11
Whole dose [Gy]:		24.00	18.00	19.20
Treatment gap [Days]:		0	0	0
BED applied [Gy]:		31.06	34.26	37.69
LOG CELL KILL :		4.05	4.47	4.92
COMPARISON OF SCHEMES				
BED reference [Gy]:		75.54	84.20	89.76
LOG CELL KILL reference:		9.85	10.98	11.70
BED applied [Gy]:		68.15	85.51	88.94
LOG CELL KILL applied:		8.89	11.15	11.60
BED residual [Gy]:		7.39	-1.31	0.82
LOG CELL KILL residual :		0.96	-0.17	0.11
TOTAL DOSE [Gy]:		64.80	56.64	57.84
TOTAL TIME [Days]:		54.00	54.00	54.00
D E F :		*0.90	1.02	0.99
	Volume :	TCP	NTCP(R)	NTCP(B)
	10 % :	0 %	0 %	0 %
	20 % :	0 %	0 %	0 %
	30 % :	0 %	1 %	0 %
	40 % :	1 %	2 %	0 %
	50 % :	23 %	3 %	0 %
	60 % :	56 %	3 %	0 %
	70 % :	76 %	* 4 %	* 0 %
	80 % :	87 %	5 %	0 %
	90 % :	93 %	5 %	1 %
	100 % :	* 96 %	6 %	4 %

Conclusion: Individual radiobiological report for a patient after treatment by the protocol (24F/1.7Gy + 4 HDR 6Gy/point A). Critical rectal and bladder dose are averaged to 75 and 80 % related to the point A. DEF = 0.90, TCP = 96%, $NTCP_{Rectum}$ = 4 % , $NTCP_{Bladder}$ = 0 %.

Application and results

A well-known protocol Phase III randomised comparison of 5 FU/CACP vs. HU as potentiators of radiotherapy in patients with stages IIB, III and IV-A Ca of the cervix with negative para-artic nodes (ID:GOD-85) has assumed application of radiation therapy:

- EBRT: 24 fraction / 1.7 Gy/ day - AP /PA open fields

- CLDR: 2 insertions / 20 Gy / „point A", gap 1-3 weeks

From the technical reasons the previous CLDR treatment has been neccessary to substitute by HDR brachytherapy treatment. The physician has proposed to apply 4 fractions with 6 Gy/„point A". External beam therapy on whole pelvis remained the same.

There is a question on place: What is an equivalent dose on HDR fraction versus LDR regime for the tumour and critical organs (bladder and rectum)?

Solution:

Entries of treatment parameters of previous LDR + EBRT (as a „users scheme") are compared with proposal HDR scheme.

From 3D-brachytherapy isodose plans we have taken maximal critical rectal and bladder percentage doses as needed input parameters to the program. The output of the program RADBIO for one specific case of dosimetric data and treatment protocol is shown at the Table 2.

To achieve a complex picture on relationships tumour response, late effects depending on dosimetric and treatment parameters the program renders these relations in graphical presentation where percentage doses on selected tissues (tumour, rectum and bladder) are variables and EBRT is applied as a fixed standard.

The results of this simulation for both protocols are shown on the Figure 4 and Figure 5.

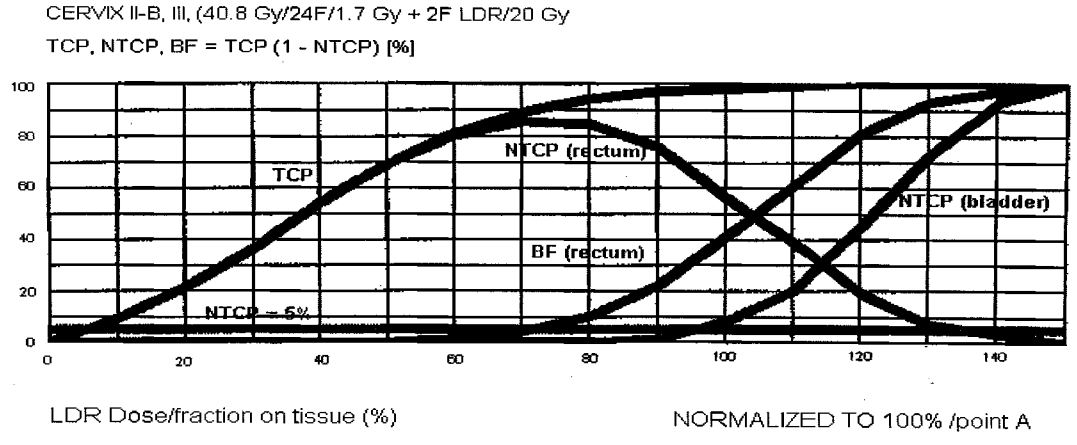

Fig.4
Therapeutic ratio for sensib. Protocol cervix II-B, III, (40.8 Gy/24F/ 1.7 Gy +F LDR/20 Gy)

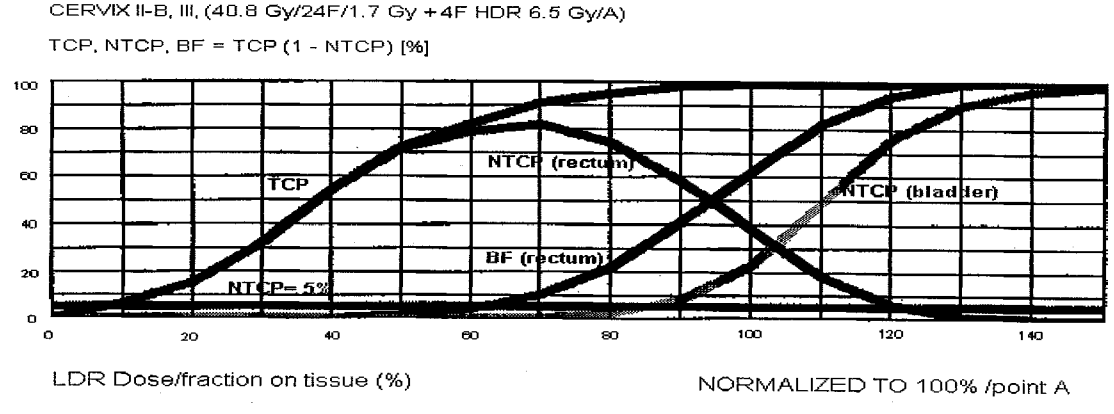

Fig. 5
Therapeutic ratio for sensib. Protocol cervix II-B, III, (40.8 Gy/2F/1.7 Gy + 4F HDR 6.5 Gy/A)

The „Therapeutic Ratio" we evaluated using so called „Benefit function" defined as:

$$BF = TCP (1 - NTCP)$$

The maximum of BF can be taken as one of the measures of the „optimal therapeutic gain" of tumour response vs. selected tissue

dose tolerance. Conclusion of simulation are summarized in Table 3.

Table 3. Critical % dose refered for isoefective regimen LDR vs. HDR

Regime	Critical % dose refered to NTCP = 5%	
	Rectum	Bladder
2Fr LDR + EBRT	60%	85%
4Fr HDR + EBRT	70%	95%

Comment:
Obviously, any changes in the EBRT are likely to have a consequential influence on the shapes and values of the critical isodoses on the rectum and the bladder.

DISCUSSION

The important point which emerges from this contribution is the strong dependence of the NTCP of particular tissues on the HDR percentage dose which they receive. Increasing the HDR percentage dose to the rectum from 70% to 80% increases the NTCP by a factor of three. Similarly, increasing the HDR percentage dose to the bladder from 85% to 95% gives a four-fold increase in NTCP.
The careful dosimetric study at Manchester, based on CT localization of the bladder, revealed that the percentage dose to this organ ranged from between 53 and 143%. Similarly, percentage dose to the rectum ranged from between 30 - 100% (Hunter et al, 1986).
The initial attempts in applying of a small number of HDR fractions (and insufficient attention devoted to dosimetric and radiobiological consequences of these high dose fractions on the normal tissues along with the tumour) have followed to unfavourable rates of late complications. There unfavourable results in HDR brachytherapy evoked scruples (doubts) about a convenience of HDR brachytherapy. These have been dispersed by the next studies and more detail dosimetric calculations and radiobiological modelling.
The availability of sophisticated 3-D software and optimized calculation software ought to allow a reduction in variances such as these, and more detailed geometric and dosimetric information about specific HDR applications can be used as a good basis for comparing actual and theoretically predicted NTCP's. DVH software is available in most advanced computer systems and may be used to provide data which can be used in more advanced radiobiological calculations, such as those available in the RADBIO program (Matula and Durovec, 1991). The program database is easily accessible in order to allow for any revisions in the values of radiobiological parameters which may emerge from future experimental and clinical analyses. It is expected that, as more reliable tolerance data becomes available, the estimated NTCP's will more closely match those determined clinically. When the data base of all radiobiological parameters is a part of the program,the entry of treatment data is simple and takes only 1 - 2 minutes of the clinicians time.

GENERAL CONCLUSION

In spite of the cautions and reservations relating to the applications of radiobiological models in the evaluation of treatment protocols and their correlation with clinical results, the concepts of BED and NTCP have their greatest impact in the following areas:

- in the initial design of new treatment schemes to match (or improve) the results of an already established protocol.
- in identifying the nature of the radiobiological parameters which have greatest influence on the treatment outcome and which need to be further investigated.
- in eliminating the imperfections of established schemes
- in providing new perspectives into the evaluation of different "rival" treatment protocols.

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